Hypoxic-Ischemic Brain Injury: Imaging Findings from Birth to Adulthood

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Global hypoxic-ischemic injury (HII) to the brain is a significant cause of mortality and severe neurologic disability. Imaging plays an important role in the diagnosis and treatment of HII, helping guide case management in the acute setting and providing valuable information about long-term prognosis. Appropriate radiologic diagnosis of HII requires familiarity with the many imaging manifestations of this injury. Factors such as brain maturity, duration and severity of insult, and type and timing of imaging studies all influence findings in HII. Severe hypoxia-ischemia in both preterm and term neonates preferentially damages the deep gray matter, with perirolandic involvement more frequently observed in the latter age group. Less profound insults result in intraventricular hemorrhages and periventricular white matter injury in preterm neonates and parasagittal watershed territory infarcts in term neonates. In the postnatal period, severe insults result in diffuse gray matter injury, with relative sparing of the perirolandic cortex and the structures supplied by the posterior circulation. Profound hypoxia-ischemia in older children and adults affects the deep gray matter nuclei, cortices, hippocampi, and cerebellum. Because findings at conventional imaging may be subtle or even absent in the acute setting, particularly in neonates, magnetic resonance spectroscopy can help establish the diagnosis of HII. Promising new neuroprotective strategies designed to limit the extent of brain injury caused by hypoxia-ischemia are currently under investigation.

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Abbreviations: ADC = apparent diffusion coefficient, ATP = adenosine triphosphate, CSF = cerebrospinal fluid, HII = hypoxic-ischemic injury, NAA = N-acetylaspartate, NMDA = N-methyl-d-aspartate, PVL = periventricular leukomalacia

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Introduction

Hypoxic-ischemic injury (HII) to the brain is a devastating occurrence that frequently results in death or profound long-term neurologic disability in both children and adults. Treatment of HII consists largely of supportive care, which does little to prevent the ongoing injury that occurs in the hours immediately following the causative insult. Promising new neuroprotective strategies designed to limit the extent of brain injury caused by hypoxia-ischemia are under investigation. Many of these treatment strategies, including hypothermia and administration of excitatory amino acid antagonists, have a limited window of effectiveness (in some cases as little as 6 hours), making early detection of injury critically important (1,2). Neuroimaging with ultrasonography (US), computed tomography (CT), and magnetic resonance (MR) imaging has become increasingly valuable in the work-up of patients with HII. As more effective treatment options become available, imaging—particularly MR imaging—has the potential to play a significant role in diagnosis and early intervention in cases of HII. In addition, imaging studies performed in the subacute stages of injury provide information on the severity and extent of injury and can be helpful in predicting long-term outcome (3–6).

Imaging findings in HII are highly variable and depend on a number of factors, including brain maturity, severity and duration of insult, and type and timing of imaging studies. Early imaging findings can be subtle and are often overlooked. Therefore, it is essential to be familiar with the many patterns of injury that may be observed and to focus attention on areas that are most likely to be injured when interpreting studies performed for suspected HII.

In this article, we review the pathophysiologic features of HII and the factors that influence the pattern of injury; review the specific imaging manifestations of HII in term (≥36 weeks gestational age) and preterm (<36 weeks gestational age) neonates, postnatal infants, children, and adults; describe the emerging role of proton MR spectroscopy in the evaluation of HII; and discuss imaging choices for the evaluation of this injury.

Pathophysiologic Processes and Factors Influencing the Patterns of Injury in HII

Regardless of the specific cause of injury, the common underlying physiologic processes that result in HII are diminished cerebral blood flow (ischemia) and reduced blood oxygenation (hypoxemia). In general, infants and children are more likely to suffer asphyxial events, which result in hypoxemia and brain hypoxia. With prolonged hypoxemia, cardiac hypoxia occurs, leading to diminished cardiac output and, ultimately, to brain ischemia. Thus, brain injury resulting from asphyxia is the consequence of ischemia superimposed on hypoxia. In fact, acute hypoxemia without superimposed ischemia is less likely to cause injury, unless the hypoxic state is prolonged (7,8). On the other hand, adults more frequently suffer brain ischemia as a result of cardiac arrest or cerebrovascular disease, with secondary hypoxia due to reduced blood flow (8).

It is well known that global hypoxic-ischemic insults do not affect all brain structures uniformly. Rather, certain tissues in the brain are more likely to be injured and are injured earlier than others, a concept known as selective vulnerability. Evidence suggests that the observed patterns of injury reflect dysfunction of selected excitatory neuronal circuits, which causes a complex cascade of deleterious biochemical events and, ultimately, selective neuronal death (7). Brain ischemia results in a switch from oxidative phosphorylation to anaerobic metabolism, which is highly inefficient. This change causes rapid depletion of adenosine triphosphate (ATP), lactate accumulation within cells, and eventual loss of normal cellular membrane function. Depolarization of presynaptic neuronal cell membranes causes a massive release of excitatory neurotransmitters—in particular, glutamate. In immature brains, glutamate binds predominantly to N-methyl-D-aspartate (NMDA) receptor–mediated calcium (Ca²⁺) channels. Activation of NMDA receptors results in an influx of Ca²⁺ into postsynaptic neurons, which triggers a number of cytotoxic processes, including activation of membrane phospholipases and production of the oxygen free radicals (such as nitric oxide) that damage cell membranes and internal constituents. Damage to mitochondria may ensue, causing further loss of ATP production and, ultimately, energy depletion. Severe energy depletion results in rapid cell death from necrosis. With lesser degrees of energy depletion, neurons may survive the initial insult, only to undergo a delayed form of programmed cell death known as apoptosis (Fig 1) (1,7–9). Apoptosis appears to play a significant role in injury to the immature brain.

From the model just described, we can draw the following conclusions: (α) the areas of the brain with the highest concentrations of glut-
mate or other excitatory amino acid receptors (primarily located in gray matter) are more susceptible to excitotoxic injury that occurs as a result of hypoxia-ischemia; (b) the areas of the brain with the greatest energy demands become energy depleted most rapidly during hypoxia-ischemia, and are therefore injured early on; and (c) because of delayed cell death from apoptosis, some injuries may not be evident until days after the initial insult has occurred. These factors help to explain the relatively specific patterns of injury that can be observed in patients with HII.

In any given patient, the sites in the brain that tend to be most vulnerable to hypoxic injury will be determined largely by the maturity of the brain, which, in turn, is a function of patient age and, in infants, gestational age at birth. This is why HII in the perinatal period (up to 1 month of age) differs from HII in adults or even in older infants and why the imaging appearance of HII differs between term and preterm neonates. One must be cognizant of the degree of brain maturity at the time of the insult when interpreting studies for suspected HII.

The severity of a hypoxic-ischemic insult also plays an important role in determining the distribution of injuries in the brain. Episodes of severe hypoxia-ischemia result in a different injury pattern compared with less severe insults. Duration of insult also seems to be a key determinant of the pattern of injury in HII, since insults of short duration usually do not result in brain injury. It has been suggested that, in the pediatric population, an arrest must typically last at least 15 minutes for brain injury to occur (10).

**HII in the Term Neonate**

HII continues to be a major cause of death and neurodevelopmental disability in term neonates, although its prevalence appears to be declining. The prevalence of HII is estimated to be between

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**Figure 1.** Diagram illustrates the cascade of events contributing to brain injury in hypoxia-ischemia. Brain ischemia results in a switch from oxidative phosphorylation to anaerobic metabolism, causing rapid depletion of ATP, lactate accumulation within cells, and eventual loss of normal cellular membrane function. Depolarization of presynaptic neuronal cell membranes causes a massive release of glutamate, which binds to NMDA receptor-mediated Ca²⁺ channels. Activation of NMDA receptors results in an influx of Ca²⁺ into postsynaptic neurons, triggering a number of cytotoxic processes, including production of the oxygen free radicals that damage cell constituents (eg, mitochondria). Mitochondrial injury causes further loss of ATP production and energy depletion. In addition, depletion of ATP further perpetuates the cycle by inhibiting the activity of ATP-dependent glutamate reuptake pumps. Severe energy depletion results in rapid cell death by necrosis. Lesser degrees of energy depletion result in apoptosis.
two and four per 1000 live term births (10). Between 15% and 20% of infants suffering HII die during the neonatal period, and an additional 25% develop permanent neurologic deficits (2).

Potential risk factors for the development of neonatal HII can be separated into antepartum, intrapartum, and postpartum factors. In most cases, HII in term neonates is associated with antepartum risk factors alone (including maternal hypotension, infertility treatment, multiple gestation, prenatal infection, and thyroid disease) or antepartum factors in combination with intrapartum factors. Intrapartum factors alone (including forcepts delivery, breech extraction, umbilical cord prolapse, abruptio placentae, tight nuchal cord, and maternal fever) are responsible for a small minority of cases of HII. Only 10% of cases of HII in term neonates are associated with postnatal complications such as severe respiratory distress, sepsis, or shock (11,12).

Clinical signs and symptoms of neonatal HII can be nonspecific at birth and usually evolve over a period of days (11), but data suggest that infants at highest risk for having suffered severe HII can be identified with reasonable reliability on the basis of a constellation of clinical findings. These findings include evidence of intrapartum distress (eg, fetal heart rate abnormality), severe functional depression (indicated by a low 5-minute Apgar score), need for resuscitation in the delivery room, severe fetal acidemia, an abnormal early neurologic examination, and an abnormal electroencephalogram (1). In the first hours following a severe insult, neonates may demonstrate depressed consciousness, periodic breathing with apnea, or bradycardia. Hypotonia may be present, particularly if there has been injury to the cortical regions, and seizures may occur in cases of severe injury (11). Infants who survive a severe hypoxic insult typically go on to develop quadriplegia, choreoathetosis, severe seizure disorders, or mental retardation. Patients with moderate injuries invariably develop spastic diplegia or quadriplegia (often falling under the umbrella term cerebral palsy) (10). In cases of mild HII, patients may recover completely or be mildly developmentally delayed.

The imaging characteristics of HII in term neonates can be subdivided based on the severity of injury (severe versus mild to moderate [partial] asphyxia). This subdivision is somewhat simplistic, since HII comprises a continuous range of insults that vary in both severity and duration. Hence, features of both severe and partial asphyxia may be seen in any given patient.

Transfontanelle cranial US is usually the first neuroimaging study to be performed in neonates with suspected HII. Although abnormalities can be detected at US, the sensitivity of this modality is low; therefore, a negative study should not be interpreted as definitive evidence that no injury has occurred. If clinical suspicion for HII remains, MR imaging should be performed to evaluate for the presence and severity of injury. It is important to keep in mind that the histologic and biochemical features of injured tissue evolve over time, so that the results of a study performed hours after an anoxic episode can differ significantly from those of a study performed several days later.

Severe Asphyxia

Severe asphyxial events in term neonates result in a primarily central pattern of injury involving the deep gray matter (putamina, ventrolateral thalami, hippocampi, dorsal brainstem, and lateral geniculate nuclei) and occasionally the perirolandic cortex. These areas of the brain are actively myelinating (an energy-intensive process) or contain the highest concentrations of NMDA receptors at term (4,13) and are, therefore, the most susceptible to neonatal HII. The remainder of the cerebral cortex is generally spared or shows mild insults, since it is generally less metabolically active in the immediate perinatal period; however, with more prolonged insults, the remaining cortex will become involved, a finding that generally portends a worse neurologic outcome (10).

Cranial US performed in the 1st week of life in term neonates has a fairly low sensitivity (~50%) for detecting abnormalities due to HII (14,15), but its sensitivity increases when it is performed after 7 days. Early US findings include a global increase in cerebral echogenicity and obliteration of the cerebrospinal fluid (CSF)—containing spaces, suggesting diffuse cerebral edema. Increased echogenicity in the basal ganglia, thalami, and brainstem can also be seen in the 1st week but is more readily apparent after 7 days (15,16). The presence of thalamic echogenicity generally suggests a more severe injury and correlates with a poorer outcome (17). Late findings include prominence of the ventricles and extraxial CSF-containing spaces, likely due to atrophy. The use of cerebral arterial Doppler US during US evaluation performed in the first few days of life may improve sensitivity and specificity for brain injury, since the presence of diminished resistive indexes (<0.6) in the anterior and middle cerebral arteries has been associated with a poor clinical outcome, even in the absence of other US abnormalities (14).
MR imaging is an accurate modality for evaluating neonatal HII. Diffusion-weighted imaging is sensitive for the detection of injury in the first 24 hours, during which time conventional T1- and T2-weighted images may appear normal. Diffusion-weighted images will demonstrate increased signal intensity in the region of the ventrolateral thalami and basal ganglia (particularly the posterior putamina), in the perirolandic regions, and along the corticospinal tracts (Fig 2). It should be noted that diffusion-weighted MR imaging performed during this period will often lead to underestimation of the ultimate extent of injury (18,19); indeed, normal findings at diffusion-weighted imaging performed in the first 24 hours, although uncommon, have been reported (18). It is believed that the prominent role of apoptosis in neonatal HII may explain why diffusion-weighted imaging in the acute setting leads to underestimation of injury. Abnormalities seen at diffusion-weighted imaging generally peak at 3–5 days and subsequently “pseudonormalize” by about the end of the 1st week (4,6,10,20), although decreased ADC values can persist in injured regions into the 2nd week (18,20). It should be noted that, although diffusion-weighted images seemingly improve and appear relatively normal by the end of the 1st week, this finding does not imply that there has been improvement or reversal of underlying disease. Hence, we use the term pseudonormalization to indicate the apparent resolution of signal intensity abnormalities on diffusion-weighted images. Because of the (admittedly unlikely) possibility of a false-negative diffusion-weighted MR imaging study early in neonatal life, a negative MR imaging study performed for HII in the first 24 hours should prompt either repeat MR imaging at 2–4 days, when diffusion abnormalities are expected to be greatest, or evaluation with proton MR spectroscopy.

Conventional T1- and T2-weighted MR images obtained on day 1 are frequently normal and are therefore less useful than diffusion-weighted images obtained for the diagnosis of HII in the acute setting. By day 2, injured areas may
demonstrate hyperintensity on both T1- and T2-weighted images (Fig 3). Signal intensity changes can also be seen in the dorsal brainstem and hippocampi (13). T2 shortening subsequently develops in the thalami and posterior putamina, usually by the 2nd week after insult (19). T1 shortening in the thalami, basal ganglia, and perirolandic cortex may persist for several months (13). The exact cause of the observed signal intensity changes seen at conventional MR imaging during the 1st week remains unclear. Suggested possible causes of T1 shortening include hemorrhage, calcification, lipid release from myelin breakdown, and even the paramagnetic effects of free radicals (13,21). Some investigators discount hemorrhage as a potential cause of early T1 shortening based on the observation that T2 shortening does not occur until several days after the initial T1 changes have occurred (19). One histologic study has reported clusters of mineralized neurons in the globus pallidus and thalamus in asphyxiated infants, findings that suggest mineralization as the cause of specific signal intensity changes on T1- and T2-weighted images (22), but this remains controversial. Furthermore, some controversy exists regarding the timing of signal intensity changes in the basal ganglia at T2-weighted imaging, with some authors reporting that T2-weighted images are usually normal during the 1st week, with T2 shortening appearing after 7–10 days (23). This discrepancy may be due to the inherently high water content of the neonatal brain, which may make subtle changes associated with edema in the acute stages of injury difficult to appreciate on T2-weighted images. In general, conventional T1- and T2-weighted images are most diagnostically useful at the end of the 1st week, when abnormalities at diffusion-weighted imaging have pseudonormalized (Fig 3). In the chronic stage of injury, atrophy of the injured

**Figure 3.** Severe neonatal HII in a 7-day-old term infant. (a) Axial T1-weighted MR image obtained at the level of the basal ganglia shows increased signal intensity in the lentiform nuclei (asterisks) and ventrolateral thalami (arrows). (b) T2-weighted MR image shows decreased signal intensity in the posterior aspects of the putamina (arrowheads) and ventrolateral thalami (arrows). (c) Diffusion-weighted MR image shows a relative lack of hyperintensity in the locations cited in b, findings that represent pseudonormalization. Only the left globus pallidus shows high signal intensity. (d) Corresponding ADC map shows hypointensity in the posterior putamina (arrowheads) and ventrolateral thalami (arrows).
structures will be seen along with T2 hyperintensity, particularly in the ventrolateral thalami, posterior putamina, and corticospinal tracts (Fig 4) (13).

When bilateral basal ganglia lesions are seen in a neonate, the primary differential diagnostic considerations are underlying inborn errors of metabolism—especially mitochondrial disorders, which should be suspected when (a) there is little clinical evidence for intrapartum hypoxia-ischemia; and (b) unusual imaging findings such as heterotopia, atrophy, or localized white matter abnormalities are seen (24).

Partial Asphyxia
Less severe insults result in a different pattern of injury. Experiments performed in animal models have demonstrated that episodes of prolonged fetal hypoxia result in shunting of blood to vital brain structures, such as the brainstem, thalami, basal ganglia, hippocampi, and cerebellum, at the expense of less metabolically active structures, namely, the cerebral cortex and white matter (25). Therefore, the brainstem, cerebellum, and deep gray matter structures are generally spared from injury in mild to moderate hypoxic-ischemic insults, since autoregulatory mechanisms are able to maintain perfusion to these areas of the brain. In neonates, moderate insults of short duration cause little or no injury to the brain (10); however, more prolonged insults result in injury to the intervascular boundary (watershed) zones, which are relatively hypoperfused as a result of this shunting. Affected patients tend to present with seizures or hypotension. Neurologic examination may eventually demonstrate proximal extremity weakness or spasticity (10).

Cranial US is of limited use in the detection of cortical and subcortical watershed zone injuries, given their location relative to the calvaria. Therefore, MR imaging is the modality of choice in term infants who experience partial asphyxial events. Again, diffusion-weighted images are the earliest to change, usually within the first 24 hours.
hours following injury, and typically demonstrate cortical and subcortical white matter restriction, most pronounced in the parasagittal watershed territories (Fig 5). It should be noted that abnormalities on diffusion-weighted images can be extremely subtle, with images even appearing normal (19), since areas of restricted diffusion can be masked by the intrinsically high T2 values of the neonatal brain, which is mostly unmyelinated. Therefore, diffusion-weighted images of the neonatal brain should always be reviewed in conjunction with their corresponding ADC maps (on which true areas of restriction should be apparent as areas of low signal intensity) or with calculated ADC values (19).

T1- and T2-weighted images may appear normal in the first 24 hours (18), but by day 2, T2-weighted images will often demonstrate cortical swelling with loss of differentiation between gray matter and white matter and hyperintensity in the cortex and subcortical white matter, predominantly in the parasagittal watershed zones but occasionally involving the hemispheres diffusely (4). The deep gray matter structures are typically spared in these patients. In the chronic stage, there is atrophy with cortical thinning and diminished white matter volume, predominantly in the parasagittal watershed zones.

**HII in the Preterm Neonate**

HII is more common in preterm neonates than in term neonates. At least 5% of infants born before 32 weeks gestational age and up to 19% of infants born before 28 weeks develop cerebral palsy. Furthermore, although preterm neonates make up a relatively small proportion of all live births, approximately 50% of cases of cerebral palsy occur in individuals born prematurely (26). The risk factors for the development of HII in preterm neonates are similar to those seen in term neonates, but injury is more likely to occur in premature patients because of both an increased frequency of events potentially causing hypoperfusion (including respiratory distress syndrome, pneumothorax, patent ductus arteriosus, and neonatal sepsis) and the relatively poor autoregulatory capacity of the premature brain (10,26).

HII in preterm infants, particularly those of very low birth weight, is difficult to diagnose clinically early on because signs may be lacking or mistaken to result from developmental immaturity. For instance, preterm infants normally have
decreased muscle tone compared with term infants (11), and transient neurologic abnormalities are especially common in preterm infants who do not go on to develop long-term neurologic deficits (26). Therefore, imaging can be particularly useful in establishing the diagnosis of HII in preterm infants.

The imaging manifestations of HII in preterm neonates differ from those seen in term neonates, due primarily to the relative immaturity of the preterm neonatal brain. Despite these differences, the observed patterns of HII in preterm neonates can still be subdivided based on the severity of the hypoxic event. Profound hypoxic-ischemic events in preterm neonates manifest predominantly as damage to the deep gray matter structures and brainstem. Events of mild to moderate severity in this population typically manifest as either germinal matrix–intraventricular hemorrhages or periventricular white matter damage (also referred to as periventricular leukomalacia [PVL]) (19,27).

**Severe Asphyxia**
The injury pattern observed in preterm neonates following brief but severe hypoxic-ischemic insults is similar in several respects to the pattern described for term neonates who suffer similar insults, but there are also characteristic differences (27). Injury to the thalami, basal ganglia, hippocampi, cerebellum, and corticospinal tracts can be seen, with the thalami, anterior vermis, and dorsal brainstem being most frequently involved. Although basal ganglia injury is frequently encountered in this group, involvement of these structures is less severe compared with involvement of the thalami, particularly among neonates born at less than 32 weeks gestation (27). When involved, the basal ganglia tend to cavitate and shrink without scarring. In addition, the perirolandic cortex is more likely to be spared in preterm neonates than in term neonates (4,27). Germinai matrix hemorrhages and periventricular white matter injury may also be seen.

The comparative resistance of the basal ganglia to damage in preterm neonates has been attributed in part to their relatively late myelination compared with the thalami (27). Pathologic studies have shown that the thalamus and globus pallidus myelinate at 24–25 weeks gestation, whereas the corpus striatum (caudate nucleus and putamen) does not myelinate until 35–36 weeks (28). The areas of most advanced myelination in the brain generally correspond to the areas of greatest metabolic activity. Consequently, these are the areas that are expected to be most susceptible to damage in the setting of oxygen deprivation. This hypothesis may also explain the relative sparing of the perirolandic cortex, which also does not myelinate until 35–36 weeks (28).

In general, because the likelihood of brain injury is high among preterm neonates and the neurologic examination is often difficult to interpret, most of these patients undergo cranial US, which can easily be performed at the patient’s bedside in the intensive care unit. US of the brain in preterm neonates with HII may demonstrate increased echogenicity in the thalami by 48–72 hours following an insult but may also be normal, particularly in the first 2 days.

MR imaging is generally the next imaging study performed after US in preterm neonates with suspected brain injury. As with asphyxiated term neonates, conventional MR imaging performed within the 1st day after injury may be normal or show only subtle abnormalities. Diffusion abnormalities are usually evident in the thalami within 24 hours (Fig 6). After 2 days, T2 prolongation can be seen in the thalami and basal ganglia. By the 3rd day following injury, T1
shortening will be seen in the injured areas. Diffusion-weighted abnormalities are most apparent around days 3–5 following insult and subsequently begin to pseudonormalize (10,19). T2 shortening develops in the injured areas at approximately 7 days, and T1 shortening persists into the chronic stage.

Mild to Moderate Asphyxia: Intraventricular Hemorrhage

The overall prevalence of intraventricular hemorrhage in preterm neonates weighing less than 2000 g is approximately 25%, and in the majority of cases this bleeding occurs within the first 24 hours of life (29,30). Prevalence is inversely related to gestational age and weight at birth; therefore, infants who are very premature with a very low birth weight are at highest risk for developing intraventricular hemorrhage. The majority of intraventricular hemorrhages in preterm neonates are associated with germinal matrix hemorrhages. The germinal matrix is a zone of cells lining the walls of the lateral ventricles in fetal life and ultimately gives rise to the neurons and glia of the brain (10,29). It is generally most active during the latter half of the 1st trimester and throughout the 2nd trimester (10). The germinal matrix becomes less active by the end of the 2nd trimester and gradually involutes over the 1st half of the 3rd trimester. By approximately 34 weeks gestation, the germinal zones have nearly completely involuted, which explains why germinal matrix hemorrhages are infrequent after this time. The last portion of the germinal matrix to involute, an area known as the ganglionic eminence, is located deep to the ependyma in the caudothalamic notch, a groove between the head of the caudate nucleus and the thalamus, and it is here that most germinal matrix hemorrhages originate.

The pathogenesis of germinal matrix hemorrhage is believed to be related to the vascular properties of the germinal matrix. Germinal matrix capillaries are unusual in that they are larger than normal systemic capillaries but are lined only with simple endothelium without the muscular or collagenous support normally seen in larger vessels (29). In addition, pathologic studies have demonstrated a greater degree of vascularity in the germinal matrix than in other portions of the brain (31). Finally, the large number of mitochondria seen within cells of the capillary walls
(three to five times more than in systemic capillaries) suggests that germinal matrix capillaries have high oxidative metabolic requirements and are, therefore, particularly susceptible to changes in oxygen concentration (29). It is believed that hypoxia-ischemia initially causes damage to the endothelial cells of the germinal matrix capillaries, resulting in loss of normal capillary integrity. With eventual brain reperfusion caused by resuscitation of the patient, hemorrhage ensues.

Germinal matrix hemorrhages have classically been subdivided into four grades, reflecting the location of hemorrhage and the presence or absence of ventriculomegaly (Table). Grade I–III hemorrhages arise from the germinal matrix, with variable extension into the lateral ventricles. Grade IV hemorrhages are not true germinal matrix hemorrhages, but rather are believed to represent hemorrhagic venous infarcts that subsequently extend into the ventricular system. Higher-grade hemorrhages correlate with a higher perinatal mortality rate and a higher prevalence of long-term neurologic sequelae (10). Intraventricular hemorrhage in neonates can generally be evaluated adequately with cranial US (Fig 7). MR imaging is generally necessary only to detect concomitant injuries in this group, such as periventricular white matter injury or deep gray matter injury.

Cerebellar hemorrhages have also been reported at autopsy in up to 25% of preterm infants with very low birth weight. With the increasing use of posterior fontanelle US, a number of these posterior fossa hemorrhages—which were probably underdiagnosed in the past, since they are often clinically silent—are being seen in preterm infants. It has been hypothesized that these hemorrhages are in fact germinal matrix hemorrhages arising from germinal zones known to exist within the external granule cell layer of the cerebellar hemispheres and in the subependymal layer of the roof of the fourth ventricle (32).

Cerebellar hemorrhages may be missed at US performed through the anterior fontanelle but are easily seen with a posterior fontanelle approach. These hemorrhages are usually lentiform or crescentic and are located peripherally in the dorsal aspects of the cerebellar hemispheres (Fig 8) (32).
Mild to Moderate Asphyxia: Periventricular Leukomalacia

Periventricular leukomalacia (PVL), also referred to as white matter injury of prematurity, is a common occurrence among premature infants. The prevalence of injury appears to be inversely related to gestational age at birth. Previously, the pathogenesis of PVL was believed to be related to ischemia in watershed zones existing in the periventricular white matter of immature brains (33). It was postulated that white matter in the immature fetal brain is supplied by ventriculopetal arteries penetrating inward from the brain surface, making the deep white matter most susceptible to decreases in perfusion; as the brain matures in the 3rd trimester, “ventriculofugal” arteries were believed to develop, shifting the watershed zone out toward the cortex. The existence of ventriculofugal arteries has come into question (34), but a recent postmortem anatomic series showed low cerebral white matter vascularity until after 32 weeks gestational age, a finding that suggests that relative hypovascularity of the periventricular white matter does, in fact, play a role in the development of PVL (31).

It is now believed that PVL is probably related to the selective vulnerability of cells of oligodendrocyte lineage to changes of hypoxia-ischemia. Prior to the onset of myelination and during the period of highest risk for PVL, the cerebral white matter is populated predominantly by late oligodendrocyte precursors known as preoligodendrocytes (35). Compared with early oligodendrocyte precursors and mature oligodendrocytes, preoligodendrocytes are more susceptible to oxidative and excitotoxic injuries occurring as a result of hypoxia (9,36). This theory is supported by the observation that the declining prevalence of PVL after approximately 32 weeks gestation coincides with oligodendrocyte maturation in the periventricular white matter (35). In addition, damage to subplate neurons—cells that play a role in normal fetal thalamocortical development and that begin to regress late in fetal development—may play a role in the development of PVL (9).

PVL is most frequently observed adjacent to the trigones of the lateral ventricles and adjacent to the foramina of Monro (33,37). Motor and visual impairment are the most common long-term neurologic sequelae of white matter injury in premature infants, due to the fact that the motor and visual pathways pass through the most commonly injured regions of white matter (10). Spastic diplegia, in which motor impairment is greater in the legs than in the arms, is a common neurologic sequela of PVL and more commonly develops in preterm infants than in term infants with HII (26).

At histologic analysis, the lesions of PVL evolve in a characteristic pattern. Initially, there is necrosis, often progressing to cavitation and the development of porencephalic cysts. Over time, these cysts collapse, eventually resulting in gliosis and significant reduction in white matter volume in the periventricular regions (33,37).

Four stages of PVL have been described at US (38). Initially, there is congestion, which manifests as globular areas of increased echogenicity (sometimes referred to as “flares”) in the periventricular regions in the first 48 hours. These findings are followed by a transient period of relative normalization, usually by the 2nd–4th weeks of life. Periventricular cyst development then occurs at approximately 3–6 weeks of life (Fig 9). Finally, by 6 months of age, end-stage PVL results, with resolution of cysts and associated ventricular enlargement (38,39).

Although increased periventricular echogenicity should raise suspicion for white matter injury, this finding is far from sensitive or predictive, since initial US studies may be normal in neonates who go on to develop PVL and, conversely, increased periventricular echogenicity may be

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**Figure 9.** PVL in a preterm infant. (a) Coronal head US image obtained in the 1st week of life shows increased echogenicity in the periventricular white matter (arrows). (b) Follow-up US image obtained 2 months later shows development of cystic changes in these regions and dilatation of the adjacent lateral ventricles, findings that are consistent with PVL.
seen in healthy neonates (33). In one study, serial cranial US examinations performed over the first 6 weeks of life in premature neonates with very low birth weight showed that the presence of prolonged (>7 days) periventricular echogenicity had a sensitivity of only 26% and a positive predictive value of only 36% for the detection of white matter injury compared with MR imaging (40). Serial US performed during this period fared considerably better in detecting subsequent cystic change (sensitivity = 75%, specificity = 100%). Therefore, the primary role of US is in detecting germinal matrix hemorrhages during the immediate postnatal period and cystic changes of PVL later in perinatal life.

MR imaging generally allows better visualization of periventricular white matter abnormalities at an earlier stage than does US, particularly among infants with noncystic areas of echogenicity at US (41). At MR imaging, early white matter injury will manifest as periventricular foci of T1 shortening (without corresponding T2 shortening) within larger areas of T2 prolongation (40). These foci are usually evident by 3–4 days, subsequently giving way to mild T2 shortening at 6–7 days (Fig 10) (10). In contrast, hemorrhage (reported to be present in 64% of cases of PVL [41]) initially manifests with much lower signal intensity on T2-weighted images. It is believed that the abnormalities seen at MR imaging represent reactive astrogliosis. Focal mineralization may account for the areas of T1 hyperintensity (22).

Head CT provides little additional information in the early stages of PVL and should probably be avoided in neonates, given the associated ionizing radiation exposure. However, CT can be useful in confirming findings of end-stage PVL later in life. End-stage PVL has a characteristic appearance at CT and MR imaging, with reduction in the volume of periventricular white matter and centra semiovale, ventriculomegaly with dilatation of the trigones, and an irregular ventricular outline. T2-weighted MR imaging will also demonstrate abnormal periventricular white matter hyperintensity, most frequently in the peritrigonal regions (Fig 11) (37,42). Thinning of the corpus callosum, particularly in the posterior body and splenium, may also be seen (42).

Figure 10. PVL in a preterm neonate. Axial T1-weighted (a) and T2-weighted (b) MR images obtained on day 4 of life demonstrate T1 hypointensity and T2 hyperintensity in the periventricular white matter. Note the punctate foci of high signal intensity on the T1-weighted image (arrows in a). These foci should be distinguished from foci of hemorrhage, which would demonstrate greater T2 shortening on the corresponding T2-weighted image.

Figure 11. End-stage PVL in a 9-year-old child who presented with motor and cognitive delay and seizures. The patient was born at 32 weeks gestational age. Axial fluid-attenuated inversion recovery MR images demonstrate increased signal intensity and a few tiny cysts in the immediate periventricular white matter. In b, there is enlargement of the atria of the lateral ventricles with a decrease in volume of the adjacent white matter, and the walls of the lateral ventricles have a wavy appearance.
HII in Postnatal Infants and Young Children

Hypoxic-ischemic injuries in infants and young children are usually the result of drowning, choking, or nonaccidental trauma (4). Certain differences exist between the patterns of injury observed in neonates and those seen in older infants; these differences are probably related to rapid brain maturation during the perinatal period. As myelination nears completion by about 2 years of age, injuries similar to the pattern seen in adults begin to appear.

Severe Asphyxia

Severe insults to infants between 1 and 2 years of age result in injuries to the corpora striata, lateral geniculate nuclei, hippocampi, and cerebral cortex (particularly the anterior frontal and parieto-occipital cortex), with relative sparing of the thalami and perirolandic cortex (13). Injuries occurring after the immediate perinatal period but before 1 year of age can demonstrate features of both birth asphyxia and later infantile asphyxia, with involvement of the basal ganglia (predominantly posteriorly), lateral thalamai, and dorsal midbrain, as well as cortical injury. The reasons for the differences between injury patterns seen in neonates and those seen in older infants are not entirely clear. It has been suggested that relative sparing of the thalami in older infants may be due to redistribution of blood flow from the anterior circulation to the posterior circulation following asphyxia, but this phenomenon would not explain the relative resistance of the perirolandic cortex in these patients (13). It is likely that some of the observed differences are due to physiologic and biochemical changes that occur with brain maturation, which result in different patterns of activity and, thus, different regional energy requirements (10).

Cranial US ceases to be a practical imaging option in infants once the anterior fontanelle has closed, which occurs as early as 4 months of age (43). Once US is no longer feasible, CT becomes the initial imaging study of choice. Early CT performed within 24 hours of an insult may be negative or may demonstrate only subtle hypoattenuation of the deep gray matter structures (13). Subsequent CT will demonstrate diffuse basal ganglia abnormalities along with diffuse cerebral edema, manifesting as cortical hypoattenuation, loss of normal “gray-white” differentiation, and cisternal and sulcal effacement (13,44,45). There may be relative sparing of the perirolandic regions (13). Hemorrhagic infarctions of the basal ganglia may be evident by 4–6 days (45). Imaging in the chronic phase will demonstrate diffuse atrophy with sulcal and ventricular enlargement (44,45).

Within the first 24 hours, a small number of these patients may demonstrate the “reversal sign,” in which there is reversal in the normal CT attenuation of gray matter and white matter (Fig 12a). It has been proposed that this finding is due to the distention of deep medullary veins secondary to partial obstruction of venous outflow from the elevated intracranial pressure caused by diffuse edema (46). The end result is that the cerebral white matter is of higher attenuation than the cortical gray matter. Another well-known CT sign of severe HII is the “white cerebellum sign” (Figs 12b, 13a, 13b) (47), which has been described in at least one study as a component of the reversal sign (48) and in which there is diffuse edema and hypoattenuation of the cerebral hemispheres with...
sparing of the cerebellum and brainstem, resulting in apparent high attenuation of the cerebellum and brainstem relative to the cerebral hemispheres. It has been suggested that this finding is due to the redistribution of blood to the posterior circulation that occurs during anoxic events (47). Both the reversal sign and the white cerebellum sign indicate severe injuries and portend a poor neurologic outcome (46–48).

MR imaging is frequently performed in children with HII. Diffusion-weighted images will usually be abnormal within the first 12–24 hours, initially demonstrating bright signal intensity in the posterolateral lentiform nuclei (Fig 13c); thalamic involvement (when present) will usually involve the ventrolateral nuclei (4). Over the next 48 hours, there is typically significant progression of involvement to include the remainder of the basal ganglia and the cortex (4). Conventional T1- and T2-weighted images obtained in the first 24 hours are often normal (13) and may appear so for up to 2 days (21). By 48 hours, T2-weighted images will usually demonstrate diffuse basal ganglia and cortical signal intensity abnormality (Fig 13d), a finding that probably represents edema (4,21). Again, there may be relative sparing of the perirolandic cortex and thalami (13).

Other entities to consider when bilateral basal ganglia abnormalities are seen include inborn errors of metabolism, hypoglycemia, osmotic myelolysis, hemolytic uremic syndrome, encephalitis, and toxic exposures (carbon monoxide and cyanide) (49).

**Mild to Moderate Asphyxia**

As in term neonates, milder anoxic events in older infants will generally result in watershed zone injuries involving the cortex and subcortical white
Figure 14. Mild to moderate HII in a 2-year-old child who suffered a hypoxic-ischemic event 5 days after undergoing a Fontan procedure. (a) Unenhanced head CT scan shows bilateral cortical and subcortical hypointensity in the parasagittal watershed regions. (b) Diffusion-weighted MR image obtained at the same level shows corresponding high-signal-intensity areas compatible with watershed infarcts.

Figure 15. HII in a 53-year-old man who experienced a prolonged, severe hypotensive episode following liver transplantation. (a, b) Axial T2-weighted MR images show hyperintensity in the globi pallidi (arrowheads in a) and cerebellum (arrows in b). (c, d) Corresponding diffusion-weighted MR images show associated high signal intensity in the globi pallidi (arrowheads in c) and cerebellum (arrows in d).

matter (Fig 14). White matter lesions are more common in children under 1 year of age (5). Relative sparing of the periventricular white matter will be seen (42).

HII in Older Children and Adults
As stated earlier, HII in adults is more often a result of cardiac arrest or cerebrovascular disease, with secondary hypoxemia. Drowning and asphyxiation remain common causes of HII in older children. Mild to moderate global ischemic insults to the brain usually result in watershed zone infarcts. Severe HII in this population primarily
affects the gray matter structures: the basal ganglia, thalami, cerebral cortex (in particular the sensorimotor and visual cortices, although involvement is often diffuse), cerebellum, and hippocampi (50,51). This predominance of gray matter injury is related to the fact that gray matter contains most of the dendrites where postsynaptic glutamate receptors are located and are, therefore, the sites most susceptible to the effects of glutamate excitotoxicity. As a result of synaptic activity, gray matter is also more metabolically active than white matter. Although cerebellar injury can be seen in neonates, it tends to be more common in older patients. The reason for this predilection is not entirely clear, but it has been suggested that the relative immaturity of Purkinje cells (which are normally exquisitely sensitive to ischemic damage) in neonates somehow protects the cerebellar cortex (52).

In older patients, CT is generally the initial imaging study performed when brain injury is suspected. CT findings include diffuse edema with effacement of the CSF-containing spaces, decreased cortical gray matter attenuation with loss of normal gray-white differentiation, and decreased bilateral basal ganglia attenuation (50). As in young children, the reversal sign and the white cerebellum sign may be seen in adults and indicate severe injury with a poor prognosis (53).

Diffusion-weighted MR imaging is the earliest imaging modality to become positive, usually within the first few hours after a hypoxic-ischemic event. During the first 24 hours, diffusion-weighted imaging may demonstrate increased signal intensity in the cerebellar hemispheres, basal ganglia, or cerebral cortex (in particular, the perirolandic and occipital cortices) (Fig 15) (51). The thalami, brainstem, or hippocampi may also be involved (5,51,54). As in younger patients, conventional T1- and T2-weighted images are often normal or demonstrate only very subtle abnormalities. In the early subacute period (24 hours–2 weeks), conventional T2-weighted images typically become positive and demonstrate increased signal intensity and swelling of the injured gray matter structures, although these findings may be subtle. As mentioned earlier, diffusion-weighted imaging abnormalities usually pseudonormalize by the end of the 1st week (4,6,10,20). Gray matter signal intensity abnormalities at conventional MR imaging may persist into the end of the 2nd week. In the chronic stage, T2-weighted images may demonstrate some residual hyperintensity in the basal ganglia, and T1-weighted images may show cortical necrosis (Fig 16), which is seen as areas of high signal intensity in the cortex (51,54).

Delayed White Matter Injury
(Postanoxic Leukoencephalopathy)
Postanoxic leukoencephalopathy is an uncommon syndrome of delayed white matter injury, usually occurring weeks after a hypoxic-ischemic event. This process occurs in approximately 2%–3% of patients following a global hypoxic insult (most commonly in association with carbon monoxide intoxication) and is characterized by a period of relative clinical stability or even improvement, followed by an acute neurologic decline, usually 2–3 weeks after the initial insult. Patients may experience delirium, personality changes, intellectual impairment, movement disorders, or, rarely, seizures (55–57). Approximately 75% of patients go on to complete or near-complete recovery over the next 6–12 months. In the remaining patients, there may be residual dementia. Rarely, the condition may progress to paresis, a vegetative state, or death (57).

In typical cases of postanoxic leukoencephalopathy, conventional and diffusion-weighted MR imaging performed immediately following the causative insult fail to demonstrate significant cerebral white matter abnormalities, but
diffusion-weighted imaging performed during the period of delayed neurologic decline demonstrates diffuse confluent areas of restricted diffusion throughout the cerebral white matter (Fig 17) (51,54,55,58–60). Corresponding hyperintensity on T2-weighted images is also seen. Although classically a delayed process, the leukencephalopathy can also manifest as progressive deterioration without an intervening lucid period. In these cases, white matter signal intensity changes can be seen within the 1st week (55). In young children, postanoxic white matter injury occurs sooner and can be observed by as early as 2 days. Clinical findings of diffuse white matter injury may not be readily apparent or may be quite subtle in very young children and infants, with abnormal MR imaging findings being the earliest evidence of white matter injury (4).

Clinical improvement appears to be associated with a decrease in the extent of signal intensity abnormalities (60), but residual abnormalities can persist beyond 18 months (61). Surviving patients may go on to develop diffuse atrophy at follow-up imaging.

The exact mechanism for delayed white matter injury following anoxia is not known. It has been suggested that the findings may represent a process similar to wallerian degeneration (51). It is also conceivable that apoptotic cell death may play a role in the pathogenesis of this entity.

**Role of Proton MR Spectroscopy in the Evaluation of HII**

Proton MR spectroscopy has become a valuable tool in the evaluation of HII, particularly in the perinatal period. Indeed, MR spectroscopy and diffusion-weighted MR imaging are the most sensitive imaging modalities for detecting HII in the acute period (19,62), and MR spectroscopy is perhaps more sensitive to injury and more indicative of the severity of injury in the first 24 hours after a hypoxic-ischemic episode, when conventional and diffusion-weighted MR imaging may yield false-negative findings or lead to significant underestimation of the extent of injury (10,18,19). MR spectroscopy will demonstrate substantial lactate elevation (appearing as a doublet centered at 1.3 ppm at 1.5 T) in the deep gray nuclei, parieto-occipital region, or white matter of the parasagittal watershed zones by as early as 2–8 hours (19,62,63). A glutamine-glutamate peak may also be detected at 2.3 ppm (62), probably reflecting the release of glutamate that occurs in HII (Fig 18).

Two lactate elevations are believed to occur during the acute to subacute period of HII. In animal models, lactate levels increase almost immediately following a hypoxic-ischemic insult, probably as a result of hypoxemia and ensuing anaerobic glycolysis, only to fall back nearly to baseline over the next few hours as a result of restored perfusion. Over the following 24–48 hours, a second increase takes place that is
thought to be the result of a process known as “secondary energy failure,” in which neurons that survived the initial insult develop delayed energy depletion, probably as a result of mitochondrial failure. This process probably explains in part why initial diffusion-weighted imaging leads to underestimation of injury in the acute setting. Injury due to secondary energy failure will result in elevated cerebral lactate after 24 hours at MR spectroscopy and carries a grave prognosis (63). In general, the finding of elevated lactate in the first few days of life portends a poor neurologic outcome (3,63).

Premature infants normally have higher lactate peaks and lower N-acetylaspartate (NAA) peaks than do term infants, which may make interpretation of the spectra of premature infants difficult. Lactate diminishes and NAA increases as the brain matures, but trace amounts of lactate may be evident even in the spectra of healthy term infants (63,64). Therefore, it helps to be aware of an infant’s gestational age at birth when interpreting an MR spectroscopic study to avoid a false-positive result (3). The lactate-NAA ratio may be a useful measure when interpreting MR spectroscopic studies performed in preterm neonates. Penrice et al (63) reported the mean lactate-NAA ratio in the thalami of control neonates (gestational age, 29–42 weeks) to be 0.25 (SD = 0.11). Asphyxiated infants (both term and preterm) tended to have lactate-NAA ratios greater than 0.4, and infants with severe injuries generally had lactate-NAA ratios greater than 0.5. Furthermore, lactate-NAA ratios above 95% confidence limits were associated with death or major impairment at 1 year (63).

In addition, some investigators have described decreased levels of NAA, centered at 2.0 ppm, in the spectra of asphyxiated infants imaged sub-acutely, a finding that also correlates with a poorer neurologic outcome (3,65). It should be noted that NAA is usually normal acutely in HII and does not significantly decline until approximately 48 hours after the acute injury (3,63). In older children, abnormal spectroscopic findings include lactate elevation, glutamine-glutamate elevation, and reduced NAA. The finding of abnormal MR imaging spectra correlates with a very poor outcome (persistent vegetative state or death) (21). A normal MR spectroscopic examination combined with normal findings at routine MR imaging generally correlates with a good outcome, although injury cannot be ruled out until day 3–4 (4).

**Imaging Choices in Evaluating HII**

A number of factors must be taken into account when choosing the most appropriate imaging study for evaluating suspected HII. These factors include, but are certainly not limited to, patient age, patient condition, and concerns about ionizing radiation exposure. A simplified algorithm for
imaging patients with suspected HII is shown in Figure 19.

Neonates with suspected HII are usually critically ill and hemodynamically unstable, making patient transport to fixed scanners often impractical in the acute setting. Therefore, cranial US is the screening examination of choice for these patients, since it is noninvasive, involves no ionizing radiation exposure, and can be performed at the patient’s bedside. The major limitations of US are its operator dependence and its relatively low sensitivity for injury, particularly over the cerebral convexities (66). Although US performed in the acute setting is helpful when it demonstrates disease, a negative US study does not rule out injury, and an alternative imaging study is often necessary.

We do not routinely advocate the use of CT in the evaluation of neonatal HII because it involves ionizing radiation exposure. Furthermore, CT is no more sensitive for detecting nonhemorrhagic injury in neonates than is US, due in part to the normally high water content of the neonatal brain (66). Therefore, MR imaging is the next imaging study of choice after US. Although MR imaging is often logistically more difficult to perform (due to issues of patient transport, sedation, and monitoring), it is more sensitive for the evaluation of HII. MR imaging protocols should include, at a minimum, axial T1- and T2-weighted sequences, diffusion-weighted sequences, and an ADC map. At our institution, we use spin-echo T1-weighted (repetition time msec/echo time msec = 600/12) and turbo spin-echo T2-weighted (6860/125) sequences. For diffusion-weighted imaging, we use a single-shot echoplanar technique with a b value of 1000 sec/mm². The optimal b value for diffusion-weighted images is controversial and varies among institutions. Most authors report using b values of 700–1000 sec/mm², although some authors report using b values as high as 1500 sec/mm² (4). If there is a concern for hemorrhage, we include an axial gradient-echo T2-weighted sequence (705/15, 20° flip angle), which is more sensitive to the presence of deoxyhemoglobin and methemoglobin than are standard turbo spin-echo T2-weighted sequences. Fluid-attenuated inversion recovery images can be useful in evaluating adults and older children but are of limited use in detecting edema in newborns.

If MR imaging performed in the first 24 hours is negative, a repeat examination performed at 2–4 days may help rule out the possibility of delayed injury, given that MR imaging may occasionally produce a false-negative result in the acute period (4). In addition, proton MR spectroscopy could be performed in the acute stage. Although some institutions routinely perform MR spectroscopy for suspected neonatal brain injury, we reserve this modality for situations in which diffusion-weighted imaging findings are normal but the clinical suspicion for HII remains high. In these situations, we perform long-echo-time (135 msec) and short-echo-time (30 msec) spectros-
copy with voxels positioned in the basal ganglia and centra semiovale. If subtle abnormalities are noted at MR imaging performed in the acute setting, follow-up imaging performed at the end of the 1st week of life may be helpful in defining progression and overall extent of injury (4).

In adults and children who are not candidates for cranial US owing to closure of the anterior fontanelle, unenhanced head CT is the initial screening test of choice. If the study is positive, no additional imaging is usually necessary, although one might consider performing additional MR imaging to assess the overall extent of injury. A negative CT study should prompt further evaluation with MR imaging because, as mentioned earlier, CT is relatively insensitive for detecting injury in the acute setting. As in neonates, repeat imaging in the subacute setting in infants and young children may be helpful in determining the ultimate extent of damage due to delayed tissue injury.

Currently, MR perfusion imaging does not play a role in the evaluation of brain injury due to global hypoxia-ischemia, although MR perfusion imaging of hypoxia-ischemia has been performed in animal models. In a rat model, Dijkhuizen et al (67) demonstrated luxury perfusion at dynamic gadolinium-enhanced MR perfusion imaging immediately following resuscitation from HII, followed by a state of mild hypoperfusion in cortical and striatal areas that persisted for several hours. By 24 hours, there was hyperemia in the caudate nucleus. Qiao et al (68) demonstrated increased regional cerebral blood flow in infarcted tissue 24 hours following hypoxia-ischemia in 4-week-old rats but not in 1-week-old rats, possibly reflecting the poorer ability of the newborn rats to mount a compensatory cerebrovascular response to hypoxia-ischemia. Although these data are of academic interest, it remains to be seen whether MR perfusion imaging will play a significant clinical role in the evaluation of HII in the future.

Conclusions
HII can pose a difficult diagnostic problem from a neuroimaging standpoint, especially in newborns. Observed injury patterns are highly variable and depend on brain maturity, severity and length of insult, and type and timing of imaging. Making the diagnosis of HII at US, CT, and MR imaging requires a clear understanding of the various imaging patterns that can result. By focusing on the specific regions that are most likely to be injured due to selective vulnerability, one can avoid false-negative interpretations caused by overlooking subtle findings in an otherwise normal-appearing brain. Diffusion-weighted MR imaging and proton MR spectroscopy are the most sensitive imaging modalities in the early hours following injury, but diffusion-weighted imaging often leads to underestimation of the true extent of injury in very young children. Therefore, delayed imaging in the subacute phase may be helpful in determining the overall extent of injury and long-term prognosis, particularly in the pediatric population.

References


Hypoxic-Ischemic Brain Injury: Imaging Findings from Birth to Adulthood

Benjamin Y. Huang, MD, MPH and Mauricio Castillo, MD

Page 418
Imaging findings in HII are highly variable and depend on a number of factors, including brain maturity, severity and duration of insult, and type and timing of imaging studies.

Page 422
In general, conventional T1- and T2-weighted images are most diagnostically useful at the end of the 1st week, when abnormalities at diffusion-weighted imaging have pseudonormalized (Fig 3).

Page 424
Abnormalities on diffusion-weighted images can be extremely subtle, with images even appearing normal (19), since areas of restricted diffusion can be masked by the intrinsically high T2 values of the neonatal brain, which is mostly unmyelinated. Therefore, diffusion-weighted images of the neonatal brain should always be reviewed in conjunction with their corresponding ADC maps (on which true areas of restriction should be apparent as areas of low signal intensity) or with calculated ADC values (19).

Page 425
Profound hypoxic-ischemic events in preterm neonates manifest predominantly as damage to the deep gray matter structures and brainstem. Events of mild to moderate severity in this population typically manifest as either germinal matrix–intraventricular hemorrhages or periventricular white matter damage (also referred to as periventricular leukomalacia [PVL]) (19,27).

Page 434
MR spectroscopy and diffusion-weighted MR imaging are the most sensitive imaging modalities for detecting HII in the acute period (19,62).
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